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PATENT APPLICATION
Docket No. 16778.5a.1.1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of		)
	Ole Thastrup et al.	)
Serial No.:	10/072,036	)
Confirmation No.:	3012	) Group Art Unit 1633
Filed:	February 5, 2002	)
For:	A METHOD FOR EXTRACTING QUANTITATIVE INFORMATION RELATING TO AN INFLUENCE ON A CELLULAR RESPONSE	)
Examiner:	Michael D. Burkhart	)
Customer No.:	022913	)

PRE-APPEAL BRIEF REQUEST FOR REVIEW

Mail Stop **Appeal**
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Reconsideration of the above-referenced application by a panel of examiners is respectfully requested in view of the following remarks.[1] Applicant again[2] respectfully cites clear error as the Examiner has (1) unreasonably omitted consideration of relevant claim elements of the presently pending claims, (2) has not established that Htun teaches each and every claim element, and (3) failed to establish a *prima facie* case of obviousness.

I. Present Invention

Currently, Applicant's patent application includes independent claims 44-46, wherein claims 44-45 define the claimed subject matter as "A method for screening a library of

[1] Please note that the following remarks are not intended to be an exhaustive enumeration of the distinctions between any cited references and the claimed invention. Rather, the distinctions identified and discussed herein are presented solely by way of example of the clear errors and omissions needed for any *prima facie* rejection.

[2] Please note that this is the second Pre-Appeal Brief Request For Review in the instant patent application. The first was requested over the Carey reference of record, which resulted in the removal of Carey in the rejections. Now Applicant makes the same request with the Htun reference which has substantially the same teachings as the Carey

compounds to detect a biologically active compound by detecting intracellular translocation of a subunit of a component of an intracellular pathway affecting intracellular processes, which subunit exhibits a biological activity of the component."[3] Each of claims 44-46 sets forth that the invention is a method that is practiced to detect biologically active compounds by "screening the library of compounds to determine whether the at least one compound of the library of compounds has a biological function or biological effect on the subunit in the one or more cells, wherein translocation of the subunit in response to the at least one compound of the library of compounds determines that the at least one compound has a biological function or biological effect on the subunit" (i.e., step (c)). The "screening" is performed in cells "containing a nucleotide sequence coding for a hybrid polypeptide comprising a luminophore linked to the subunit" (i.e., step (a)) The hybrid polypeptide is used as a tool in a novel method for monitoring the translocation of the subunit, where the luminophore merely provides a means of observing the intracellular translocation of the subunit, and a compound is determined to have a biological effect on the subunit when translocation of the hybrid polypeptide is observed. Thus, the claimed invention is a new use of the hybrid polypeptide tool.

Compounds that are known to have an effect on the subunit are excluded because of the known biological activity on the subunit, and thereby one cannot "detect' or "determine" whether a compound has an effect that is already known. The invention is **NOT** a method of determining whether a compound that has a known biological effect on the subunit also has the same or similar biological effect on the hybrid polypeptide.

II. The Htun Reference

Applicant respectfully submits that the Htun reference teaches a hybrid polypeptide (GFP-GR) that has a luminophore (GFP) fused to a rat glucocorticoid receptor (GR). Htun investigated the GFP-GR hybrid polypeptide to determine whether it could be used as a tool. In order to determine whether the tool worked for its intended purpose (e.g., provide visual data of GR), Htun tested the translocation of GFP-GR in response to compounds that had a known effect on the translocation of GR. Compounds having known translocation effects on GR were used to

reference. Both the Htun and Carey references teach the same thing: determining that well known compounds having well known effect on GR have substantially the same effect on the GFP-GR fusion polypeptide.

[3] Claim 46: "A method for screening a library of compounds to detect a biologically active compound by detecting intracellular translocation of a subunit of a biologically active polypeptide affecting intracellular processes, which subunit exhibits a biological activity of the polypeptide." Examiner has yet to establish that GR is a subunit of a biologically active polypeptide, and for this reason *prima facie* anticipation of claim 46 has not been established.

determine whether the compounds would have the same effect on GFP-GR so that the effects on GR could be used as a control to be compared with the effects on GFP-GR. Htun found that the GFP-GR hybrid polypeptide had translocation properties similar to GR, and thereby could provide visual data of GR.

While Htun teaches that GFP-GR can be a tool, Htun does not teach or suggest specifically using the tool to screen a library of compounds to determine whether a compound has an effect on GR. In fact, Htun teaches that "the presence of GFP" appears not to have affected normal GR function" (page 4849, first column). The only prophetic uses of the GFP-GR hybrid polypeptide described by Htun include, "GFP-GR should serve as an invaluable tool for understanding further details of receptor activation, the translocation process, interaction of receptors with components of the eukaryotic interphase nuclei, and mechanisms of transcriptional activation by steroid receptors" (page 4850 first column, last paragraph). Nothing in Htun indicates, teaches, or suggests that the GFP-GR is sufficient or suitable for screening a library of compounds to determine whether a compound has an effect on GR.

Therefore, in no instance does Htun teach or suggest that the GFP-GR can be used for screening a library of compounds to determine whether a compound has a biological function or biological effect on the subunit (e.g., GR) in the one or more cells." Thus, Htun teaches a useful tool, but does not teach or suggest the specific use of the tool in screening compounds to determine whether a compound has a biological function or biological effect on GR.

III. 102 Rejection

The Examiner has committed clear error in asserting that the Htun reference[4] anticipates claims 44-46 because each and every element of the independent claims have not been found in the Htun reference, as they were not found in the Carey reference.[5] The Examiner has stated that Htun clearly determined that "GR-GFP was or was not translocated in response to several steroid library members,"[6] and that "[t]his is all that is required to meet the claim step (c) in, for

[4] In view of evidence of Carey or Agarwal, both of record.
[5] Applicant's position is that the teachings of the Htun reference are substantially similar to the Carey reference in that both teach the use of known compounds with known effects on GR in order to determine that the GFP-GR functions substantially similar to GR. As such, the teachings of Htun and Carey are only a validation that the GFP-GR responds in the same manner as GR when exposed to known compounds having known effects on GR. Neither Htun nor Carey "screen" a compound with GFP-GR to determine whether or not the compound has an effect on GR. Only compounds with known effects on GR are used in both Htun and Carey.
[6] The only compounds tested on the GFP-GR in Htun were all well known and characterized as ligands for GR. There is no library of compounds disclosed in Htun. The small number of compounds, each having a well documented effect on GR, were only tested on GFP-GR to show that GFP-GR translocated substantially as GR

instance, claim 44."[7] Applicant respectfully disagrees because such an analysis is contrary to establishing a *prima facie* anticipation, and it does not take into account each and every element of step (c), as recited above. Specifically, Htun does not teach or suggest, "**screening the library of compounds to determine whether the at least one compound of the library of compounds has a biological function or biological effect on the subunit in the one or more cells**."

Additionally, the Examiner stipulates that "the compounds used by Htun et al had a known effect on GR,"[8] which illustrates Applicant's assertion that Htun does not teach or suggest at least step (c) of the independent claims. If the Examiner stipulates that the compounds of Htun had known effects on GR, how is it that the Examiner alleges that Htun anticipates the claimed invention? Surely testing a small number of known compounds with known effects on GR is not screening a library of compounds to determine whether a compound has an effect on GR; such effects were already known for GR and thereby could not be "determined" in Htun.

Therefore, Htun clearly does not teach or suggest each and every element of step (c), as recited in independent claims 44-46, and thereby does not anticipate these claims. Additionally, Htun does not teach or suggest the preamble of claims 44-46 for the same reasons it does not teach or suggest step (c). As the Examiner is aware, it is established that a "claim is anticipated only if each and every element set forth in the claim is found, either expressly or inherently, in a single prior art reference."[9] Since the Examiner has (1) admitted that Htun does not screen compounds to determine an effect on GR, and (2) affirmatively asserted that each and every claim element of step (c) does not need to be shown in Htun,[10] the Examiner has committed clear error in asserting Htun anticipates claims 44-46.[11]

IV. 103 Rejection

The Examiner has committed clear error in asserting that the combination of references[12] teaches or suggests each and every element of the claims 44-46 because each and every element of the independent claims have not been found in or suggested by the combination of references.

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translocates in response to the individual compounds. No compounds in Htun were tested on the GFP-GR that had unknown effects on GR.

[7] Office Action mailed 2/19/2009, page 4.

[8] Office Action mailed 2/19/2009, page 6.

[9] *Vedegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

[10] See above regarding footnotes 5-8.

[11] The Examiner has not established that GR is a subunit of a biologically active polypeptide, and thereby Htun cannot anticipate claim 46.

The Examiner relies on Htun teaching or suggesting at least the preamble, step (a), and step (c) of claims 44-46 for the alleged *prima facie* case of obviousness because none of Agarwal, Sonenberg, and/or Dunlay teach or suggest at least the preamble, step (a), and/or step (c).[13] As shown above, since Htun does not teach or suggest at least the preamble and/or step (c)[14] of claims 44-46 and none of the other references in the combination teach or suggest the preamble, step (a), and/or step (c), the combination of references necessarily does not teach or suggest the preamble and/or step (c). When none of the references in a combination of references teaches a claim element, then the combination of references as a whole cannot teach the claim element, and thereby a *prima facie* case of obviousness has not been established.

While Htun teaches that GFP-GR is a tool, Htun does not teach or suggest a method of using the tool as presently claimed in claim 44-46. Since none of the other references in the combination[12] teach or suggest any method of using the GFP-GR tool, they cannot provide teachings or suggestions that are missing in Htun. Conversely, while Agarwal and/or Sonenberg and/or Dunlay may teach or suggest some types of "screening," none of these references teach or suggest the "screening" of step (c) or the desire or benefit of performing a method as recited in the preamble.

Therefore, the combination of references recited by the Examiner clearly does not teach or suggest each and every element of presently pending claims 44-46. Thus, the Examiner has committed clear error in asserting the combination of references establishes a *prima facie* case of obviousness for claims 44-46.[15]

Dated this 4th day of May, 2009.

Respectfully submitted,

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[12] The combination of references is: Htun (with evidence of Carey), Agarwal, Sonenberg, and Dunlay.
[13] For example: Agarwal does not teach the preamble, step (a), and/or step (c), Sonenberg does not teach the preamble, step (a), and/or step (c); and Dunlay does not teach the preamble, step (a), and/or step (c), and thereby the combination of references cannot teach any of the preamble and/or step (c).
[14] Applicant admits on the record that Htun teaches step (a) of claims 44-45, but not claim 46.
[15] Applicant additionally asserts that the references have been combined through the use of impermissible hindsight and without a valid reason. There is no logical nexus to combine Htun, Agarwal, Dunlay, and Sonenberg without the benefit of first reading the Applicant's application. Additionally, at the time of invention, nobody used fusion polypeptides in screening a library of compounds to detect biologically active compounds, and that is why Applicant is entitled to a patent on the presently claimed invention.